REMARKS

Claim 34 remains rejected under 35 U.S.C. §112, first paragraph, for allegedly containing new matter. In this regard, the statements in the Office action maintain the position that the priority date of the subject matter recited in claim 34 is May 26, 2000, the filing date of the present application. Applicants respectfully traverse and request withdrawal of the rejection.

The priority date of claim 34 is, at the very least, November 27, 1998, the International filing date of PCT/JP98/05348, because the present application is a national stage filing of, and therefore identical to, PCT/JP98/05348. Further, the identity of the present specification with that of PCT/JP98/05348 was established by the translator's verification filed May 26, 2000. The translator's verification of the English language specification has not been challenged. Therefore, it is not clear to Applicants how claim 34 can be assigned an effective date of May 26, 2000 rather than the International filing date of November 27, 1998, when the two disclosures are identical.

The Office action states that there is no teaching in PCT/JP98/05348 that the claimed molecule is obtained by PCR or RT-PCR amplification using specifically SEQ ID Nos. 21 and 22 as primers. However, as described above, PCT/JP98/05348 is identical to the present application, which discloses the use of the recited primers for amplification in Example 3 on page 30, first paragraph. Since PCT/JP98/05348 is identical to the present application, it also discloses the use of the specifically recited primers for amplification in Example 3. See the attached copy of page 21 of the published PCT that clearly recites primer sequences 21 and 22. Accordingly, the present

application was appropriately filed as a §371 national phase filing of PCT/JP98/05348, and the priority date of claim 34 is, at the very least, November 27, 1998, the filing date of the PCT application.

While it is unclear that the position set forth in the Office action is that the specification fails to teach the subject matter of claim 34, regardless of the date of the specification, we will address this concern as well. The Office action states that "there is no teaching ... that the claimed nucleic acid molecule is obtained by PCR or RT-PCR amplification using specifically SEQ ID NOS: 21 and 22 as primers." Claim 34 is drawn to the set of nucleic acids that result from amplifying with primer sequences 21 and 22. Therefore it is unclear to what the Office action is referring to as "the claimed nucleic acid."

Claim 34 does not specify that the so amplified nucleic acids have the capacity to encode a protein that exhibits Rho-GEF activity. The context of this aspect of the invention is to amplify DNA whatever its make-up might be. This aspect of the invention includes nucleic acid allelic mutants which may in fact be incapable of exhibiting Rho-GEF activity. In addition, this aspect of the invention is associated with screening to identify which cells, and at which stage of development, cells express DNA that can be amplified by the specific primers. See the following disclosures in this regard as examples of the discussion of such nucleic acids: original claim 6, the paragraph bridging pages 3 and 4, page 5, lines 15-19, Figure 6, the paragraph bridging pages 16 and 17, the first complete paragraph on page 17, Example 3 in its entirety and the paragraph bridging pages 34 and 35. This list is intended to be exemplary of the descriptive support of this

claim rather than exhaustive or complete. The specification clearly describes the set of nucleic acids set forth in claim 34 as well as specific and credible utilities for this set of nucleic acids. There is no basis upon which the rejection can rely for the position that the written description must be so extensive that in each instance that an embodiment is exemplified extra words must be added to link the embodiment with the remainder of the disclosure. The examiner is requested to consider the subject matter of original claim 6 and recognize that pending claim 34 is an embodiment of original claim 6.

In view of the above remarks, reconsideration and withdrawal of the new matter rejection is respectfully requested.

Claims 26, 28 and 32 were rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking written description of a "fragment" that encodes at least ninety consecutive amino acids of SEQ ID No. 2 or a "fragment" that is complementary to a nucleic acid that encodes at least ninety consecutive amino acids of SEQ ID No. 2 or a kit containing such fragments.

Claims 26 and 28 have been amended to exclude nucleic acids that encode proteins that are unrelated to the class of proteins that exhibit the structural and functional characteristics that are described in the specification.

Applicants respectfully request reconsideration and withdrawal of the written description rejection in view of the amendment to claims 26 and 28.

Claims 15-17, 27 and 32 were rejected for allegedly lacking a clear written description of a "gene" or a "DNA sequence" encoding SEQ ID No. 2 or variants thereof having Rho-GEF activity. According to the Office Action, the specification fails to

describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, since the claimed invention encompasses the gene. The Office Action also asserts that the structures of regulatory elements and untranslated regions are empirically determined as shown by Harris *et al.*, Ahn *et al.* and Cawthon *et al.*, and therefore determination of these structures is not conventional in the art. Accordingly, one skilled in the art would allegedly not recognize from the disclosure that Applicant was in possession of a gene or DNA sequence as claimed. Applicants respectfully disagree.

Applicants respectfully note that Harris *et al.*, Ahn *et al.* and Cawthon *et al.* were each published well before the priority date of the present invention and are in fact evidence that those of skill in the art routinely identified regulatory regions and untranslated elements even for complex genomic loci. Therefore, in contrast to what is alleged in the Office Action, these references are further evidence that determination of regulatory elements and untranslated regions was indeed conventional in the art at the time the invention was made. According to the Written Description Guidelines (FR, Vol. 66, No. 4, page 1099, January 5, 2001) such common techniques need not be described, because one of skill in the art would be familiar with such techniques and would incorporate such knowledge into his understanding as to what the inventor possessed at the time of filing.

To illustrate, in the Federal Register publication of the Written Description Guidelines for Examination, the Office answered one comment by stating that "[a]ctual reduction to practice may be crucial in the relatively rare instances where the level of

knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally, or specify a process of making a composition by naming components and combining steps" (with emphasis, see page 1101). In fact, the Guidelines state at page 1106 that:

> An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (With emphasis.)

Applicants have identified a novel gene sequence, CDEP-1, and have described its function in differentiated chondrocytes. Thus, Applicants have described the relevant identifying characteristics of the novel gene. Isolation of the regulatory regions of the genomic sequence was conventional at the time the application was filed and one of skill in the art would clearly consider the Applicants to be in possession of the genomic sequence at the time the application was filed.

In view of the remarks above, reconsideration and withdrawal of the rejection of claims 15-17, 27 and 32 under §112, first paragraph for lack of written description is respectfully requested.

Claims 16 and 17 remain rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement for DNA sequences encoding variant proteins having Rho-GEF activity falling within the scope of the claim. According to the Office Action,

although one could screen for the variant proteins, Applicant has not shown how to make the claimed variants. Applicants respectfully traverse the rejection.

Respectfully, the position presented in the Office Action dated August 26, 2003, is entirely inconsistent with the position set forth in the previous Office Action dated January 6, 2003. In the Office Action dated January 6, 2003, the Examiner acknowledged that methods for replacing, deleting and inserting particular amino acids to make variants is well known in the art. However, the Examiner noted that the function of the claimed variants was not recited in the claims, and without a known function, one would not know how to screen for the claimed variants. (See page 8 of the Office Action dated January 6, 2003).

In the Reply filed July 2, 2003, Applicants amended the claims to recite that the claimed variants had Rho-GEF activity, and pointed to disclosure in the specification regarding screening for this activity. (See page 11 of Reply filed July 2, 2003). Now the Examiner responds by arguing that although one could screen for variant proteins, Applicant has not shown how to make the claimed variants. However, the Examiner has already acknowledged in the Office Action dated January 6, 2003, that methods for replacing, deleting and inserting particular amino acids to make variants are well known in the art. Thus, the current position is entirely inconsistent with previous prosecution. This presents an injustice to Applicants who have earnestly attempted to respond to the Examiner's concerns only to be faced with a basis for the rejection which was already withdrawn in a previous Office Action.

In any case, to repeat Applicants' arguments submitted in the Reply filed March 19, 2002:

> At pages 13-14 of the specification, applicants disclose that any known method may be used for replacing, deleting or inserting particular amino acid residues, including ordinary genetic engineering methods as disclosed in Sambrook et al. (1989), which is a well known genetic engineering manual. A preferred method is provided by Hill's "The Proteins," which was published in 1979 (see page 14, lines 5-15). Further, applicants provide a list of conservative amino acid substitutions that are most frequently tolerated in proteins, and also define the domains most important for the function of CDEP. And, as described on page 14 (lines 3-5), those of skill in the art could easily select appropriate mutant proteins having functions comparable to CDEP.

In view of the Examiner's previous acknowledgment in the Office Action dated January 6, 2003, that methods for making the variants are well known, and in view of the Examiner's acknowledgment in the Office Action dated August 26, 2003, that one could screen for the claimed variants, Applicants believe that the rejection should be withdrawn. In view of the remarks above, as well as all arguments made in previous Replies, Applicants respectfully request withdrawal of the rejection of claims 16-17 for scope of enablement under 35 U.S.C. §112, first paragraph.

Claims 15-17 and 32 remain rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. According to the Office Action, the rejection remains because although one could screen for the claimed gene or DNA sequence, Applicant has not shown how to make the claimed gene or DNA sequence. Further, the Examiner asserts that the structure is not known and not predictable as taught by Harris *et al.*, Ahn *et al.* and Cawthon *et al.* Applicants respectfully traverse the rejection.

The Examiner notes in the Office Action that the recitation of Sambrook *et al.* is acknowledged (page 6 of the Office Action dated August 26, 2003). However, the Examiner does not appear to have considered Sambrook for its teachings. In contrast to what is alleged in the Office Action, Sambrook teaches a method for isolating the flanking regions of a gene sequence, not a method of screening. Therefore, Applicants fail to understand how the Examiner's statements regarding screening are responsive to the points raised in Applicants' previous Reply.

To repeat the arguments made in the Reply filed July 2, 2003:

> [I]t would not require undue experimentation to identify such sequences based on the disclosure combined with the level of skill in the art. For instance, at page 18, lines 12-19, it is disclosed that genes encoding a CDEP protein may be isolated following southern blot hybridization using a probe based on the disclosed amino acid and nucleotide sequences. In addition, at page 17, lines 5-7, it is disclosed that a CDEP gene can be obtained from chromosomal DNA by PCR or hybridization using oligonucleotide primers or a probe based on the disclosed nucleotide sequence.
>
> Further, according to Sambrook *et al.*, 1989, Molecular Cloning: A Laboratory Manual (2d edition) (relevant pages attached hereto), libraries generated from mammalian genomic DNA had been in use since the mid-1970's for cloning mammalian genes (see page 9.2). And according to the teachings on page 9.3, it was well-known at the time this Manual was published that one could use libraries of randomly cleaved DNA to "walk" along the eukaryotic chromosome starting with a single specific probe, in order to isolate segments of DNA in and around target sequences without knowledge of the location of surrounding restriction sites. Thus, it was common practice at the time the present application was filed to isolate a genomic DNA corresponding to a known cDNA sequence following hybridization of a probe to a genomic library. Moreover, such common techniques need not be described, because the specification need not disclose what is common knowledge in the art. (pages 13-14, with emphasis)

The Examiner also asserts that the structure of regulatory and untranslated regions of the gene sequence would not be predictable as taught by Harris *et al.*, Ahn *et al.* and

Cawthon *et al.* However, these references were published well before the priority date of the present invention. Harris *et al.* was published in 1995, Ahn *et al.* was published in 1993 and Cawthon *et al.* was published in 1991. Accordingly, these references show that the skilled artisan routinely identified regulatory regions even for complex genomic loci several years prior to the present invention. Applicants fail to understand how the Examiner can argue that the skilled artisan would not be able to isolate the regulatory and untranslated regions of the CDEP-1 gene, when clearly those of ordinary skill in the art had been isolating and characterizing even complex genomic loci for many years prior to the present invention as evidenced by the cited art.

In view of the above remarks, Applicants respectfully request withdrawal of the rejection of claims 15-17 and 32 under 35 U.S.C. §112, first paragraph. If the Examiner should maintain the rejection, then Applicants respectfully request that the Examiner respond to the points raised in Applicants' Reply so that prosecution may be moved along in a productive manner.

Claim 34 was rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Koyano *et al.*, which was published on December 18, 1997. Applicants respectfully request that the rejection be withdrawn, since the priority date of claim 34 is at the very least the filing date of the priority PCT application, or November 27, 1998, for the reasons discussed above in response to the allegation that claim 34 constitutes new matter.

Further, with respect to the teachings of Koyano *et al.*, the disclosure of Japanese priority document contains the recitation of SEQ ID NO:1 which is the teaching relied

upon in Koyano *et al.* See page 6 of the English-language translation of JP 1997-342060 as well as SEQ ID NO:1 therein. While claim 34 is a genus, the Koyano *et al.* reference teaches only the single species that is identical to disclosed SEQ ID NO:1. In this instance in the context of a rejection under 35 U.S.C. § 102(a), an applicant need only show prior completion of the invention of the species disclosed by the reference. See, for example, *In re Spiller*, 182 U.S.P.Q. 614 (CCPA 1974) in this regard. Since the species SEQ ID NO:1 is clearly evidenced by Japanese application 1997-342060 to which priority is claimed herein, a §102(a) rejection of claim 34 would be improper, since the priority document establishes at least a constructive reduction to practice of the species invention as of November 27, 1997 before the publication date of the Koyano *et al.* reference.

This reply is fully responsive to the Office Action dated August 26, 2003. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted,

DATE: **February 26, 2004**

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etus 社製)を用いた。

また、軟骨組織から抽出した totalRNA0.5μg から逆転写反応を行い、CDEP の塩基配列に基づいて設計した上流特異プライマー(5'-TCACTTCGTGGTTTCAGAGC-3')および下流特異プライマー(TCGTCTTCGCTCTCCTCAAT-3')を用いて増幅反応を行い、CDEP cDNA 断片を得た。増幅反応条件は、変性反応（95℃、1 分間）、アニーリングおよび伸張反応（65℃、3 分間）に設定し、20 回増幅した。得られた DNA を 1%アガロースゲル上で、100V、15 分間電気泳動した。

PCR サザンブロット法は、以下のように行った。すなわち、電気泳動したゲル中の DNA を 1.5M NaCl を含む 0.5N NaOH 溶液中で変性させた後、6xSSC を用いてナイロンメンブレン Nytran0.45(Schleicher&Schuell 社製）に転写した。このメンブレンを、Oligolabelling Kit(Pharmacia Biochem 社製）により標識した [^{32}P] 標識 CDEP プローブを含んだハイブリダイゼーション溶液中で、68℃、16 時間のハイブリダイゼーション反応を行った。反応後、メンブランを洗浄し、オートラジオグラフィーを行った。放射活性測定には BAS2000 Image analyzer(Fujix 社製)を使用した。

ウサギ肋軟骨成長板軟骨細胞の培養は以下のように行った。すなわち、4 週齢雄性日本白色家兎の肋軟骨から成長板を分離し、それらを 0.1%EDTA、0.1%トリプシン含有 PBS および、0.05%コラゲナーゼ含有 DMEM にて消化し、軟骨細胞を単離した。6well 組織培養用プレートに、1well あたり 30 万個の細胞を播種し、10%ウシ胎仔血清を含むアルファ MEM にて培養した。培地交換は、培養 5 日目より 2 日毎に行った。

ウサギ肋軟骨成長板軟骨細胞培養系における CDEP mRNA の発現は、培養 6、10、14、18、22、26 日目に細胞層から totalRNA を抽出し、CDEP mRNA の発現レベルを RT-PCR 法にて検討した。

ウサギ肋軟骨成長板軟骨細胞培養系における PTH による CDEP mRNA の誘導は、培養 6、10、14、18、22、26 日目に PTH(1-84)($1x10^{-7}$M)を添加し、さらに 24 時